HOUSE DUST MITE, DERMATOPHAGOIDES FARINAE - dermatophagoides farinae injection
HOUSE DUST MITE, DERMATOPHAGOIDES PTERONYSSINUS - dermatophagoides pteronyssinus injection
Allermed Laboratories, Inc.

WARNINGS

This product is intended for use by physicians who are experienced in the administration of allergens extracts or for use under the guidance of an allergy specialist. The initial dose must be based on skin testing as described in the dosage and administration section of this insert. Patients being switched from alum-absorbed or other types of precipitated extracts or non-standardized extracts to this extract should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if symptoms occur. As with all allergenic extracts, severe systemic reactions may occur and in certain individuals these reactions may be life-threatening or cause death. Patients should be observed for at least 20 minutes following treatment. Emergency measures as well as personnel trained in their use should be immediately available in the event of a life-threatening reaction. Patients being switched from one lot of extract to another from the same manufacturer should have the dose reduced to 25 percent.
Patients receiving beta-blocking drugs may be refractive to the usual dose of epinephrine, in the event that epinephrine is required to control an adverse allergic reaction to this product.
This product should never be injected intravenously. See also the WARNINGS, and ADVERSE REACTIONS Sections below.

DESCRIPTION

Mite extract is a sterile solution containing the extractables of mite whole bodies in 0.25% sodium chloride, 0.125% sodium bicarbonate, 50% glycerol by volume and 0.4% phenol as a preservative. The mites are grown on a medium of yeast and pork and are handled and cleaned in a manner to remove more than 99% of the food medium. The medium contains no material of human origin. This extract may be administered by the scratch, prick-puncture, or intradermal methods of skin testing for diagnostic purposes and subcutaneously for therapeutic purposes as directed under Dosage and Administration.
Intradermal skin tests in patients who were puncture test positive (Sum E ≥ 40 mm) to either *D. farinae* or *D. pteronyssinus* extract were performed with extracts of the mite food medium obtained from the same supplier. The results, submitted to the FDA by several manufacturers, were as follows: By intradermal testing, there was 1 positive (Sum E ≥ 20 mm) in 44 individuals at an estimated 1% level of medium content (approximately the same as contained in the mite extract). At a ten-fold increase (estimated 10% medium content), 4 positives in 40 individuals were observed. Two of the individuals who were skin test positive to the mite extract and who also were skin test positive to the medium extract were also skin test positive to an extract of yeast (Saccharomyces sp.) when tested by the puncture method.
The extract is standardized by comparing its relative potency by ELISA competition to a U.S. reference mite extract available from the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. The U.S. reference extract has been assigned a potency of 10,000 AU/mL based on quantitative skin testing[1].

CLINICAL PHARMACOLOGY

The mechanism for the pharmacologic action of allergenic extracts used diagnostically is based on the liberation of histamine and other substances when the allergen reacts with IgE antibody attached to mast cells. The mechanism of the therapeutic effect is not well understood and further research is required to substantiate current hypotheses.
Mites belonging to the genus Dermatophagoides are found in approximately 80% of house dust samples throughout the world[2,3]. *D. farinae* is common in much of the United States[3], although *D. pteronyssinus* is predominant in certain coastal regions and both species are commonly found in homes [4,5].
The diagnosis of mite allergy is established by the allergy history and skin test reactivity [6,7].
Immunotherapy with mite extract has been studied by several investigators. It is generally believed that hyposensitization with this product is helpful in reducing symptoms associated with house dust allergy [8,9].

INDICATIONS AND USAGE

Standardized mite extract is indicated for use in the diagnosis of patients with a history of allergy to mites or house dust and for the treatment of patients with a history of mite allergy who have established sensitivity to mites by diagnostic skin testing.
The use of mite extract for the above purposes should be made only by physicians with special familiarity and knowledge of allergy as described in a standard allergy textbook [10].

CONTRAINDICATIONS

Injections of mite extract should not be administered in the presence of diseases characterized by a bleeding diathesis. Immunotherapy should not be started in patients until a specific diagnosis of Type I allergy to mite is made by a physician based on skin testing with this product.

Other contraindications include:
EXTREME SENSITIVITY TO MITE: Determined from previous anaphylaxis following skin testing, immunotherapy, or natural exposure.
AUTOIMMUNE DISEASE: Individuals with autoimmune disease maybe at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease.
MYOCARDIAL INFARCTION: Patients who have experienced a recent myocardial infarction may not be able to tolerate immunotherapy. The benefit-to-risk ratio must be carefully evaluated.
CHILDREN WITH NEPHROTIC SYNDROME: Children with nephrotic syndrome require careful consideration and probably should not receive immunotherapy due to a variety of seemingly unrelated events that may cause an exacerbation of nephrotic disease.

WARNINGS
Concentrated extract must be diluted with sterile diluent prior to first use on a patient for treatment or intradermal testing. All concentrates of allergenic extract are manufactured to assure high potency and therefore have the ability to cause serious local and systemic reactions, including death in sensitive patients [11]. Patients should be informed of this risk and precautions should be discussed prior to initiating immunotherapy (see PRECAUTIONS below).
Allergenic extract should be temporarily withheld from patients or the dose adjusted downward if any of the following conditions exist: 1) severe symptoms of rhinitis and/or asthma; 2) infection or flu accompanied by fever; 3) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection.
The dosage must be reduced when starting a patient on fresh standardized mite extract or when transferring a patient from non-standardized or modified extract to standardized extract, even though the labeled strength of the old and new vials may be the same. This is necessary due to a loss of extract potency during storage in the physician's office. The mite allergen content of old and new extract may be compared and adjusted by dosage reduction and/or dilution before the new extract is administered. The amount of new extract given should not exceed 25% of the last dose given from the old vial, assuming both extracts contain comparable amounts of mite allergen. Any evidence of a local or generalized reaction requires a reduction in dosage during the initial stages of immunotherapy, as well as during maintenance therapy.
Beta-blocking drugs may make patients refractory to the usual dose of epinephrine, in the event epinephrine is required to treat an adverse allergic reaction.

PRECAUTIONS
GENERAL:This product should not be injected intravenously. The risk of severe allergic reactions can be minimized by taking a careful history and by the use of scratch or prick-puncture testing prior to intradermal testing. If the scratch or prick-puncture test is negative, an intradermal test with a one hundred-fold dilution of the concentration used for scratch or prick tests usually is safe. If there is a history of unusual sensitivity or if the scratch or prick-puncture test is not performed first, a more dilute solution such as 1:10,000 v/v of the concentrate should be used initially for intradermal testing.
Systemic allergic reactions may occur as a result of immunotherapy. The risk can be minimized by adherence to a careful injection schedule, which starts with a low concentration of extract and is increased slowly. The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so. Extracts should not be administered by the patient or other individuals who are not prepared to treat anaphylaxis should it occur.
A separate sterile tuberculin syringe graduated in 0.01 mL should be used for each injection.
Antihistamines and hydroxyzine can significantly inhibit the immediate skin test reaction (see DRUG INTERACTION).
INFORMATION FOR PATIENTS: Because most serious reactions following the administration of allergenic extracts occur within 20 minutes of the injection, the patient should remain under observation for this period of time. The size of the local reaction should be recorded, because increasingly large local reactions may precede a subsequent systemic reaction with increasing dosage. The patient should be instructed to report any unusual reactions to the attention of the physician. In particular, this includes swelling and/or tenderness at the injection site or reactions such as rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness or faintness.
Caution should be exercised in testing or treating pregnant females because a systemic reaction might conceivably cause uterine muscle contractions leading to abortion.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long term studies in animals have not been conducted with allergenic extracts to determine their potential for carcinogenicity, mutagenicity or impairment of fertility.
PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with mite extract. It is also not known whether mite extract can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Mite extract should be given to a pregnant woman only if clearly needed.
PEDIATRIC USE: Although standardized mite extract has not been studied in children, unstandardized extract of *D. farinae* has been administered by the prick test to asthmatic children ages 1 to 16 without any reported adverse response [6]. Extract of *D. pteronyssinus* has been given subcutaneously for hyposensitization to children ages 5 to 14 with adverse reactions being limited to local discomfort, redness and swelling for one or two, days [7].
NURSING MOTHERS: It is not known whether allergenic extracts are excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when allergenic extracts are administered to a nursing woman.

DRUG INTERACTION: Antihistamines and hydroxyzine can inhibit the immediate skin test reaction. Patients being treated with delayed absorption antihistamine tablets should be free of such medication for 48 hours before testing. Non-sedating antihistamines, such as terfinadine and astemizole, may variable suppress the skin response for longer periods of time. Epinephrine injection inhibits the immediate skin test reaction for several hours.
Beta-blocking drugs may make patients refractory to the usual dose of epinephrine, in the event epinephrine is required to treat an adverse allergic reaction.

ADVERSE REACTIONS
Adverse systemic reactions usually occur within minutes and consist primarily of allergic symptoms such as generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema and hypotension. Less commonly, nausea, emesis, abdominal cramps, diarrhea and uterine contractions may occur. Severe reactions may cause shock and loss of consciousness. Fatalities have occurred rarely [11]. Systemic reactions occur with varying frequency in different clinics. To some extent, the reaction rate is related to the type and dose of administered extract and to the degree of sensitivity of the patient. Despite all precautions, occasional reactions are unavoidable. Reports from regulatory authorities in Sweden to the Center for Biologics Evaluation and Research (CBER) indicated that several deaths have been associated with the use of mite extracts. CBER was subsequently informed that these deaths may have been related to use by physicians or other health professionals untrained in the administration of potent allergens, rather than a product defect. It should be noted that anaphylaxis and deaths following the injection of mite and other extracts also have been reported by the British Committee on Safety in Medicine in the British Medical Journal, 293: 943, 1986.
Local reactions consisting of erythema, itching, swelling, tenderness and sometimes pain may occur at the injection site. These reactions may appear within a few minutes to hours and persist for several days. Local cold applications and oral antihistamines may be effective treatment. For marked and prolonged local reactions, steroids may be helpful.
The treatment of systemic allergic reactions is somewhat dependent upon the symptom complex. Epinephrine hydrochloride 1:1,000 aqueous, in an adult dose of 0.3 - 0.5 mL (or 0.01 mL per kg. for children) administered subcutaneously in the opposite arm is the immediate treatment of choice. A tourniquet should be placed above the site of the extract injection if the injection was done on the extremities. Antihistamines may offer relief of recurrent urticaria, associated skin reactions and gastrointestinal symptoms. Persistent wheezing may necessitate intravenous aminophylline treatment. For profound shock and hypotension, intravenous fluids, vasopressors and oxygen also may be needed. Maintenance of an open airway is critical if upper airway obstruction is present. Corticosteroids may provide benefit if symptoms are prolonged or recurrent.

OVERDOSAGE
A strong local reaction to the injection of extract may be treated with oral antihistamines and the local application of a cold compress. The dosage must be reduced and additional extract must not be given until all evidence of the reaction has disappeared. A systemic reaction following the injection of extract must be treated immediately with Epinephrine hydrochloride 1:1,000 aqueous (see Adverse Reactions, paragraph 4 above).

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The product should be discarded if discoloration or particles are observed.
The skin test concentration of 10,000 AU/mL in dropper vials is used for scratch or prick-puncture testing. Puncture tests performed with *D. farinae* extract on 5 persons sensitive to mite showed a mean diameter wheal of 8.8 mm ± 1.8 mm and mean diameter erythema of 39.2 mm ± 5.3 mm.
Puncture tests with *D. pteronyssinus* extract on 10 persons sensitive to mite showed a mean diameter wheal of 7.8 mm ± 4.1 mm and mean erythema of 33.7 mm ± 12.0 mm.
Extract for intradermal testing should be prepared by diluting the 10,000 AU/mL stock concentrate in bulk vials with sterile saline with or without human serum albumin.
Intradermal skin tests (0.05 mL) in persons highly sensitive to mite showed the following results:
AU/mL to elicit 50 mm sum of diameter erythema reaction

Allergen	No. of Persons	Mean	Range
D. farinae	5	0.0040	0.0013-0.0124
D. pteronyssinus	10	0.0031	0.0001-0.1416

Intradermal extract should be used as follows:
Intradermal tests should only be performed after a scratch or prick-puncture test has been administered with a negative result. Patients who do not react to a valid scratch or prick-puncture test should be tested intradermally with 0.02 to 0.05 mL of a 10 AU/mL (1:1,000 v/v of the 10,000 AU/mL concentrate). If this test is negative, a second intradermal test may be performed using a 100 AU/mL (1:100 v/v dilution of 10,000 AU/mL concentrate). Skin tests are graded in terms of the wheal and erythema response noted at 1 5 to 20 minutes. Wheal and erythema size may be recorded by actual measurement of the extent of both responses.

Therapeutic

The dosage of mite extract administered by subcutaneous injection is highly individualized and varies according to the degree of sensitivity of the patient, his clinical response and tolerance to the extract administered during the early phases of an injection regimen. In patients who appear to be highly sensitive by history and skin test, the initial dose of the extract should be 0.05 mL of a 0.1 AU/mL dilution or as established by skin test titration. The amount of allergenic extract is increased at each injection by not more than 50% - 100% of the previous amount, and the next increment is governed by the response to the last injection. Large local reactions which persist for longer than 24 hours are generally considered an indication for repeating the previous dose or reducing the dose. Any evidence of systemic reaction is an indication for a significant reduction (at least 50%) in the subsequent dose. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of the concentrate may be painful due to the glycerin content of the extract.

The optimal interval between doses of mite extract has not been definitely established. However, as is customarily practiced, injections are given one or two times per week until the maintenance dose of extract is reached. At this time, the injection interval may be increased to 2 weeks, then to 3 weeks and finally to 4 weeks. If the patient does not return for 6 to 8 weeks after the last injection, the dose should be reduced to 25% of the last dose. If longer than 8 weeks, a dose reduction of one, too or three dilutions may be made depending on a consideration of the components and the patient's sensitivity The dosage and the interval between injections may need to be modified according to the clinical response of the patient. When switching patients to fresh extract, the initial dose should be reduced to one-quarter (25%) of the previous dose.

The usual duration of treatment has not been established. A period of three to five years of injection therapy constitutes an average course of treatment.

Children and older age patients appear to tolerate injections of allergenic extract well, and no special recommendations need to be made for these groups.

Preparing Dilutions

To prepare dilutions for intradermal skin tests and therapeutic use, the stock concentrate may be diluted as shown in Table 1. Vial #1 is made by adding 1.0 mL of the concentrate to 9.0 mL of sterile diluent. Vial #2 is made by adding 1.0 mL of Vial #1 to 9.0 mL of sterile diluent. This process is repeated until the desired concentration is achieved. In each case, the subsequent vial is made by adding 1.0 mL of the previous dilution to 9.0 mL of sterile diluent. The number of allergy units per mL in each dilution is shown in table below.

Volume per volume dilutions of 5,000 AU/mL and 10,000 AU/mL concentrates to provide a ten-fold dilution series.

Vial No.	**w/v Dilution of Concentrate**	**5,000 AU/mL Concentrate** ***AU/mL***	**10,000 AU/mL Concentrate** ***AU/mL***
1	1:100,000	0.05	0.1
2	1:10,000	0.5	1.0
3	1:1,000	5.0	10.0
4	1:100	50.0	100.0
5	1:10	500.0	1,000.0
6	No Dilution	5,000.0	10,000.0

HOW SUPPLIED

Extract of *D. farinae* and *D. pteronyssinus* containing 5,000 and 10,000 Allergy Units per mL is supplied in 50% glycerol v/v in 10 mL, 30 mL and 50 mL vials. Extract containing 10,000 Allergy Units per mL is supplied in 50% glycerol v/v in dropper vials for scratch or prick-puncture testing. An equal v/v mixture of the two mites is offered in 10, 30 and 50 mL vial sizes at a concentration of 2,500 AU/mL or 5,000 AU/mL for each mite. See DESCRIPTION above for the complete list of the active and inactive ingredients of this product.

Extract of *D. farinae* and *D. pteronyssinus* may be diluted in sterile buffered saline containing 0.4% phenol or in sterile buffered saline containing human serum albumin and 0.4% phenol.

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